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**Case Report**

# Human Papilloma Virus Infection and Anal Cancer in Kidney Transplant Recipient

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**Abstract:** Human papillomavirus (HPV) infection is one of the most common sexually transmitted infections worldwide and causes anal cancer. The incidence of HPV infections in renal transplant recipients is 17% to 45%. Using immunosuppression treatment has been associated with significantly lower risks of de novo malignancies and viral infections after kidney transplantation. We reported the results of switching Tacrolimus to Sirolimus in a kidney transplant recipient who suffered from severe cutaneous warts.

**Keywords:** Kidney Transplantation, Human Papilloma Virus, Ano-Genital Neoplasms

## 1. Introduction

Kidney transplantation is the best replacement therapy in patients with end-stage renal disease (ESRD). However, long-term results have not improved in the last decade, probably as a consequence of the adverse effects of immunosuppressive (IS) drugs. IS medications are a leading cause of graft loss in the long term. They substantially predispose to infections and de novo *neoplasms*. Most malignant neoplasms are lymphoma and skin cancers; however, many authors have also noted a high rate of ano-genital neoplasms in renal allograft recipients [1].

Infections are an important cause of morbidity and mortality in renal transplant recipients [2].

Initially it was theorized that IS agents were the cause of carcinogenesis; however, because of their ability to induce alterations in DNA, Human Papilloma virus (HPV) infection was recently identified as the leading cause of cervical neoplasia. The immunosuppression treatment may predispose to development of HPV infection with potential to progress to cancer [1].

HPV are ubiquitous viruses that infect the skin of the majority of immune competent and immune-compromised individuals [3].

Given the T-lymphocyte dysfunction inherent to transplantation IS, viral infections are particularly increasing [2].

The incidence of HPV infections in renal transplant recipients is 17% to 45% [1].

Oncogenic types of HPV can cause cancer of the cervix, vagina, vulva, penis, anus and a subset of cancers of the head and neck [4].

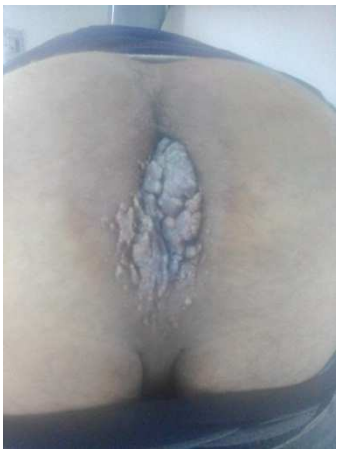
Cutaneous warts, caused by the HPV, are very common among these patients, and they may progress to squamous cell carcinoma. Viral warts in immune-compromised patients are frequently recurring and current therapies are of limited efficacy. Some reports are available on the effectiveness of modulating IS regimens in the treatment of viral warts in

organ transplant recipients. New agents such as Sirolimus and Everolimus, belonging to mammalian target-of-Rapamycin (mTOR) inhibitors, have been successfully used in preventing organ rejection after transplantation. Using these agents has been associated with significantly lower risks of de novo malignancies and viral infections after kidney transplantation [5].

Here, we reported the results of switching Tacrolimus to Sirolimus in a kidney transplant recipient who suffered from severe cutaneous warts.

## 2. Patient and Observation

A 47-year-old man with ESRD due to unknown nephropathy received a preemptive living- related kidney transplant in 2013. The IS therapy consisted of Tacrolimus 0.2 mg/kg/d; Mycophenolate Mofetil 1 g/d and prednisolone 7.5 mg/d. In 2015, the patient experienced multiple genital warts (Figure 1). Pelvic and abdominal MRI showed a cauliflower-like tumor of the anal margin measuring 53 x 20 x 54 mm invading the internal sphincter and having intimate contact with the external sphincter without direct sign of invasion. Biopsy shows condylomata acumination the anal region. The diagnostic was genital HPV infection. It was contracted through anal sex. He received a conservative surgery. Since the warts did not improve, Tacrolimus was replaced with Sirolimus, 2 mg/d. The warts gradually disappeared (Figure 2) within 3 months. They completely disappear at 1 year and renal function remained stable at 103µmol/l.



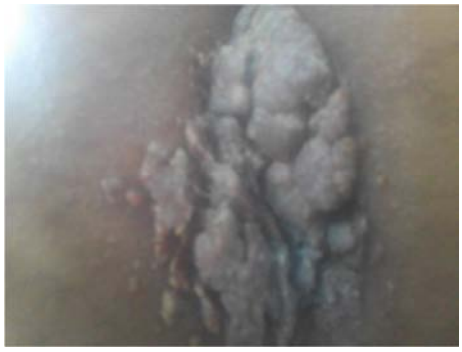


***Figure 1.*** *Genital warts in a kidney transplant recipient.*

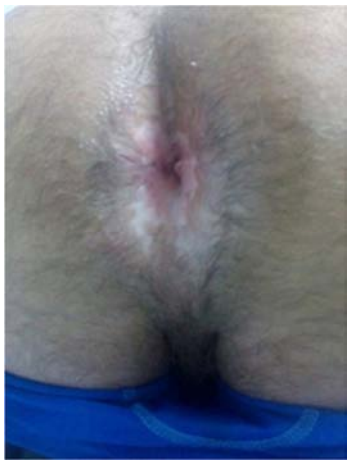


***Figure 2.*** *Improvement of the warts after conversion of Tacrolimus to Sirolimus.*

## 3. Discussion

The risk of infection in a renal transplant recipient is determined by the interaction of the epidemiologic exposure, the timing, intensity, and virulence of the organisms, and the patient's "net state of immunosuppressant," which reflect a measure of all host factors contributing to the risk for infection [2].

As a result of epidemiological factors and intensified IS, the spectrum of opportunistic infections in solid organ transplant recipients has become more diverse now, including some rare viruses. HPV is increasingly seen in organ transplant recipients presenting with warts and condylomata acuminata, as well as neoplastic manifestations which may potentially lead to anal, vulvar, cervical or penile carcinoma. HPV is known to play a crucial role in the development of non-melanoma skin cancers, which show a markedly incidental increase in the long-term follow-up after organ transplantation [6].

HPV infection causes warts in different parts of the body. More than 40 different strains of HPV affect the genital area. Some types of HPV can cause cancer of the cervix. Vaccines can protect against the strains of genital HPV most likely to cause genital lesions or cervical cancer. Genital warts may appear as flat lesions, small cauliflower-like bumps, or tiny stem-like protrusions. In men, genital lesions may appear on the penis and scrotum or around the anus, as in our patient. In women, genital warts appear most commonly in the vulva but may also occur near the anus, on the cervix, or in the vagina. HPV infection occurs when the virus enters the body through a cut, abrasion, or small tear in the outer layer of the skin. The virus is transferred primarily by skin-to-skin contact. Genital HPV infections are contracted through sexual intercourse, anal sex as in our patient, and other skin-to-skin contact in the genital region. Genital warts occur most often in adolescents and young adults, such as our patient. People who have weakened immune systems owing to immune system-suppressing drugs used after organ transplants, as our patient, are at greater risk of HPV infections. HPV infection is diagnosed after visual inspection of the lesions. Genital

lesions are treated with Podofilox, a topical product that destroys genital wart tissue. If the lesions are extensive, they should be physically removed by freezing with liquid nitrogen, burning with electrocautery, surgical removal, as in our patient, or laser surgery followed by Podofilox applications [2].

The role of calcineurin inhibitors, widely used following organ transplantation, in the genesis of viral diseases, and notably HPV-associated warts, is well established [7]. Taking into account the properties of mTOR inhibitors, we successfully tempted Sirolimus conversion. MTOR inhibitors are currently used in the prevention of rejection following kidney and more recently liver transplantation. Several lines of evidence suggested that these drugs may be useful in the prevention of de novo tumors and the treatment of malignancies because of anti-proliferative and cytostatic properties. Recent studies have suggested that mTOR inhibitors may interfere with the replication of different types of herpes viruses (cytomegalovirus, herpes virus 8, Epstein-Barr virus) and retroviruses (human immunodeficiency virus). Indeed, clinical trials showed significant lower incidence of cytomegalovirus infection following heart, liver, and kidney transplantations, while in vitro experiments showed that this effect was at least in part mediated through inhibition of the phosphatidylinositol-3-kinase (PI3k)/protein kinase B (Akt) pathway, an upstream activator of mTOR which plays a key role in viral replication. Since HPV activates the PI3k/Akt pathway, it is tempting to hypothesize that mTOR inhibitors may alter HPV pathogenesis and thereby improve the course of warts. After conversion to Sirolimus and calcineurin inhibitor withdrawal, amino-transferase levels returned to normal and the cosmetic benefit appeared after a few weeks: initially with significant modifications in the thickness and color of the warts, followed by a reduction in their number, leading to overall improvement in this dermatological complication [7].

Case reports are available on improvement of cutaneous warts after conversion of the IS regimen from calcineurin-inhibitors to mTOR inhibitors. In a kidney transplant recipient with widespread skin warts, Kostaki and colleagues converted Tacrolimus to Sirolimus, which led to a significant regression of the lesions within 5 months. Another report by Dharancy and colleagues on a liver transplant recipient showed regression of cutaneous warts after converting calcineurin inhibitors and Mycophenolate Mofetil to Sirolimus monotherapy [5].

Trials of prophylactic HPV vaccines have been very effective in those unexposed to the HPV types included in the vaccine. The vaccines use components of the major HPV capsid proteins (L1 alone or in combination with L2) which self-assemble into virus-like particles (VLP). VLP induce neutralizing antibodies which protect the individual before exposure to HPV infection. There are two prophylactic HPV vaccines currently available. One is a quadrivalent vaccine (HPV types 6, 11, 16 and 18) and the other is a bivalent (HPV types 16 and 18) vaccine. Because the quadrivalent vaccine also includes HPV types 6 and 11 which are the major causes of genital warts, clinical trials have demonstrated over 90% efficacy in preventing warts caused by the four HPV types included in the vaccine in both women and men. In addition, trials of the quadrivalent vaccine have shown 78% efficacy in anal intraepithelial neoplasia; preventing incident anal intraepithelial neoplasia; among men who have sex with men. Only the quadrivalent vaccine has been widely studied in males, with only limited immunogenicity data for the efficacy of the bivalent vaccine in boys. The schedule of the quadrivalent vaccine is three doses at time 0, and at months 2 and 6. There are limited safety and efficacy data specifically in the transplant population. However, given that the HPV vaccines do not contain live virus, we suggest vaccination of transplant patients using similar guidelines as above. There are also no data on whether vaccination would increase the likelihood of allograft rejection. There is some evidence in the HIV-infected population that the HPV vaccine is safe and immunogenic [8].

## 4. Conclusion

Current evidence suggest that conversion of the IS regimen from calcineurin inhibitors to mTOR inhibitors can be helpful in the treatment of transplant recipients with severe skin warts. Further investigations are needed to prove these results and clarify the underlying mechanisms. Future studies of safety, immunogenicity, and efficacy of prophylactic HPV-vaccines among transplant patients are needed to clarify the benefit of HPV-vaccination in this population.

## Competing Interests

Any competing interests.

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